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Greater reductions in nicotine exposure while smoking very low nicotine content cigarettes predict smoking cessation

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ABSTRACT

Objective Reducing the nicotine content of cigarettes is a potential regulatory strategy that may enable cessation. The present study investigated the effect of nicotine exposure while smoking very low nicotine content (VLNC) cigarettes on cessation outcomes. The roles of possible sources of nicotine were also explored, including the VLNC cigarette and co-use of cigarettes with normal nicotine content.

Methods A secondary data analysis of two analogous randomised trials of treatment seeking, adult daily smokers (n=112) who were instructed to smoke VLNC cigarettes for 6 weeks and then make a quit attempt. Controlling for baseline demographic and smoking features, the association between reductions in nicotine exposure during the 6-week trial, assessed by urinary total cotinine and biomarker-confirmed smoking abstinence 1 month later, was tested. Subsequent analyses controlled for the effects of the frequency of VLNC and normal nicotine content cigarette use and the nicotine yield of the VLNC cigarette (0.05 vs 0.09 mg).

Results Greater reductions in nicotine exposure while smoking VLNC cigarettes predicted abstinence independent of individual differences in baseline smoking, cotinine, dependence, gender and study. Nicotine reduction was largest among individuals who were assigned to smoke a VLNC cigarette with lower nicotine yield and who smoked fewer normal nicotine content and VLNC cigarettes.

Conclusions In the context of nicotine regulations and corresponding research, factors that undermine nicotine reduction must be addressed, including the availability and use of cigarettes with normal nicotine content and not sufficiently reducing the nicotine yield of cigarettes. Maximising nicotine reduction may facilitate smoking cessation.

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According to the WHO Framework Convention on Tobacco Control (Article 9), guidelines may be developed to regulate the content and emissions of tobacco products.[1] As nicotine in tobacco sustains smoking,[2] reducing the nicotine content in cigarettes could improve public health by increasing cessation rates.[3 4]

The potential impact of nicotine regulations on smoking has been evaluated using very low nicotine content (VLNC) cigarettes. VLNC cigarettes contain much less nicotine in the tobacco and when smoked, yield substantially less nicotine (<0.1 mg)[3] than conventional cigarettes (eg, 0.8 mg).[5–7] Within a week of switching to VLNC cigarettes, smokers have markedly reduced levels of nicotine metabolites that are similar to abstinent smokers[8 9] and remain low with continued use.[10 11]

Reduced nicotine exposure from VLNC cigarettes, however, have not consistently facilitated cessation. Among treatment-seeking smokers, 6 weeks of VLNC cigarettes use alone or with nicotine replacement therapy increased cessation in some[11–13] but not all investigations.[10] Specifically, after smoking VLNC cigarettes alone, only 24.1% of participants were abstinent, compared with 35.9% in an analogous study.[11] Understanding what processes enable smoking cessation is critical to explain any underestimated effects of VLNC cigarettes on abstinence and to determine the impact of nicotine reduction as a regulatory strategy. To this end, the present study examined if lower nicotine exposure improved cessation rates when smoking VLNC cigarettes. Factors that may undermine nicotine reduction efforts and corresponding abstinence rates were also explored, including the co-use of conventional cigarettes, the nicotine yield of VLNC cigarettes and the number of VLNC cigarettes smoked.

METHODS

Participants

Treatment-seeking, adult daily smokers were recruited from the community via advertisement as part of two larger studies (N_{2010}=165; N_{2013}=235) comparing the effect of VLNC cigarettes (0.05–0.09 mg nicotine yield) on smoking outcomes to other nicotine-containing products (eg, 0.3 mg cigarettes, lozenge, patch).[10 11] Eligible participants smoked 10–40 cigarettes per day (CPD). Exclusion criteria included pregnancy/nursing, unstable physical/psychiatric conditions, contraindications for medicinal nicotine use and recent other tobacco/nicotine product use. The University of Minnesota Institutional Review Board approved the studies.

The present study examined individuals assigned to use VLNC cigarettes only and used the products for at least 1 week (n=112). Participants were generally Caucasian (83.9%) and middle-aged (mean=44.75 years, SD=12.88), with equally represented genders (47.3% male). Original publications provide additional details.[10 11]

Procedure

Participants experienced nearly identical protocols, except that most individuals in the later study (76%) smoked 0.09 mg nicotine yield cigarettes because the original 0.05 mg cigarettes were

unavailable. After smoking the usual brand cigarettes for a 2-week baseline period, participants were instructed to smoke the VLNC cigarette exclusively for 6 weeks. The participants were provided with 150% of their baseline CPD and reported cigarette use using a daily diary. They were encouraged to report (and not penalised for) non-study cigarette use. A weekly, brief standardised counselling session prepared participants for a quit attempt at the end of the study. Both studies evaluated biomarker-confirmed abstinence at week 12 (6 weeks postquit attempt).

Measures

Nicotine exposure at baseline, weeks 6 and 12 was assessed by total urinary cotinine (urinary free cotinine plus cotinine *N*-glucuronide).[14] Change in cotinine was examined in two ways: week 6 cotinine level controlling for baseline cotinine level and per cent change in cotinine level from baseline to week 6. The cotinine outcomes were natural log transformed due to the positive skew.[i]

Abstinence at week 12 was defined as no VLNC or non-study cigarettes smoked during the past 7 days and carbon monoxide <6 ng/mL. The analyses were replicated using cotinine (<35 ng/mL) to confirm self-reported abstinence. These analyses are omitted for brevity because they yielded similar findings and identical conclusions.

Analyses

Using logistic regression (Mplus V.7.11), the association between the change in cotinine levels and week 12 biomarker-confirmed abstinence from cigarettes was examined. Missing data at week 6 were handled using the maximum likelihood estimation with Monte Carlo data generation. Individuals lost to follow-up after week 1 were coded as smoking at week 12. A second set of analyses accounted for sources of nicotine at week 6. Specifically, VLNC cigarette type (0.05 vs 0.09 mg), week 6 non-study and VLNC CPD, and study non-compliance (ie, any self-reported non-study nicotine\tobacco use after week 2) were added as predictors of both change in cotinine and week 12 abstinence. Other tobacco product use was not considered due to infrequent use (n=2). Covariates included baseline cotinine, CPD and Fagerström Test for Nicotine Dependence score excluding CPD item (FTND), gender and study (2010 as the reference category).[15]

RESULTS

At baseline, participants smoked 20.09 CPD (SD=1.76) and were moderately nicotine dependent (FTND=4.46, SD=1.76). The retention rate was 74% for week 6 and 63% for week 12. Table 1 summarises the observed relations between cotinine levels and study outcomes.

The lower urinary total cotinine level after smoking VLNC cigarettes for 6 weeks increased the odds of cessation 6 weeks later (OR=0.52, 95% CI 0.34 to 0.80, p=0.003). This effect was replicated with per cent change in cotinine (OR=0.46, 95% CI 0.27 to 0.79, p=0.005).[ii iii] Effects were not moderated by study or gender (ie, non-significant interaction terms).

Controlling for other covariates and sources of nicotine exposure, the week 6 urinary total cotinine level was significantly higher in the 2010 study (standardised:β=−0.29, p=0.046) and among individuals who smoked 0.09 mg VLNC cigarettes (β=0.31, p=0.03), reported more non-study (β=0.34, p=0.001) and VLNC (β=.26, p=0.01) CPD at week 6 and was marginally associated with non-compliance (β=0.18, p=0.09). The week 6 urinary total cotinine level continued to predict abstinence (OR=0.44, 95% CI:0.22–0.86, p=0.03), after controlling for sources of nicotine exposure. Per cent change in cotinine was significantly associated with non-study (β=0.43, p<0.001) and VLNC CPD at week 6 (β=0.22, p=0.045). Per cent change in cotinine remained significantly related to abstinence (OR=0.39, 95% CI 0.18–0.86, p=0.007), after controlling for sources of nicotine.

CONCLUSIONS

Greater reductions in nicotine exposure when smoking VLNC cigarettes were associated with increased cigarette abstinence. This is consistent with previous research[11–13] and literature reviews[16 17] indicating that reducing the nicotine content of cigarettes may improve public health.

The extent of nicotine reduction was affected by the co-use of conventional cigarettes with normal nicotine content. Individuals who smoked conventional cigarettes exhibited higher nicotine exposure, which corresponded with difficulty in quitting smoking (6.3% quit relative to 51.2% who reported only using VLNC cigarettes). Smoking conventional cigarettes most likely maintained the reinforcing properties of cigarettes and nicotine dependence, undermining the effect of VLNC cigarettes on cessation. Thus, research conducted in an open marketplace with widespread availability of conventional cigarettes may underestimate the impact of nicotine reduction due to non-compliance. Research should utilise methods to reduce non-compliance (eg, incentivising compliance, limit access to conventional cigarettes) and report how non-compliance impacts study findings.

Similarly, characteristics of VLNC cigarette use, such as its nicotine yield and number smoked per day, increased nicotine exposure. While the nicotine yield of the VLNC cigarettes was substantially reduced relative to conventional cigarettes (0.8 mg), almost doubling their nicotine yield (from 0.05 to 0.09 mg) along with an increased smoking rate could sustain nicotine exposure at a level that impedes cessation. This may partially explain the differential outcomes in previous research.[10 11] Thus, to facilitate cessation in research and regulatory context, it is imperative to sufficiently lower the nicotine yield of cigarettes.

Several study limitations should be acknowledged. The sample of completers was relatively small and not nationally representative, which limits the generalisability of findings. Non-completers were assumed to be smoking, which may have underestimated cessation rates. Non-compliance was self-reported. Thus, associations between non-compliance and cessation may have been underestimated, leading to a continued association between cotinine and cessation. As a post hoc secondary analysis that did not experimentally manipulate nicotine exposure was conducted, associations may be partly explained by unmeasured individual differences in compliance, motivation or environment (eg, spousal smoking, smoke-free policies) that also affect cessation. This issue was partly addressed by controlling for baseline characteristics associated with cessation (eg, FTND, CPD, cotinine). Furthermore, the nicotine yield of the

[i]Per cent change was transformed (absolute value of per cent change −101) in order to conduct the natural log transformation on a distribution with a positive skew with values ≥1.
[ii]Analyses were replicated after excluding participants who dropped out of the study prior to week 6. The pattern of findings was successfully replicated for both outcomes.
[iii]Analyses with per cent change excluded three outlier week 6 cotinine cases (at least 3 SDs from the mean).

Table 1 Key sample characteristics (n=83) at each observed week 6 cotinine level

	Natural log of week 6 cotinine									
	0	1	2	3	4	5	6	7	8	9
Sample size	2	0	1	2	16	21	24	6	5	6
Percentage in 2013 study	100		100	0	56.3	47.6	75.0	83.3	100	66.7
Percentage smoking 0.09 mg yield	0		100	0	25.0	33.3	70.8	66.7	60.0	66.7
Study CPD (week 6)	0		2.6	7.9	8.7	16.9	17.8	17.2	11.4	18.0
Non-study CPD (week 6)	0		0	0	0	0	0.2	0.7	4.2	6.7
Percentage non-compliant	0		100	0	12.5	14.3	33.3	50.0	80.0	66.7
Percentage abstinent (week 12)	100		100	100	81.3	57.1	47.1	16.7	20	16.7

Participants who completed the week 6 visit (n=83) were divided into 10 groups based on their natural log of week 6 cotinine levels (binned by rounding to the nearest whole number). Each column in the table provides descriptive statistics (means or proportions) of study outcomes for individuals who had the specified cotinine level (refer to sample size for n). The data provide qualitative support for factors that may explain the linear relation between cotinine level and quit rates. Of note, only two participants stopped smoking the very low nicotine content (VLNC) cigarettes before week 6 because they had quit smoking all cigarettes. Furthermore, the number of VLNC cigarettes appeared to differentiate individuals at cotinine level 4 from those at cotinine level 5, whereas non-compliance and a higher nicotine yield of the study cigarette (0.05 mg vs 0.09 mg) appeared to differentiate individuals at cotinine level 5 from those at cotinine level 6.
CPD, cigarettes per day.

assigned VLNC cigarette predicted abstinence rates, reinforcing the importance of nicotine in quit rates.

Finally, additional research is needed to determine how nicotine exposure from other tobacco products would impact cessation. Until now, many investigations of VLNC cigarettes, including this study, have excluded individuals who regularly use other tobacco or nicotine products. With the evolving marketplace of non-combustible products, including the increasing popularity of e-cigarettes, it is critical to determine how VLNC cigarettes may be more or less effective in this real-life context. While the present study suggests that nicotine from conventional cigarettes may undermine cessation while smoking VLNC cigarettes, it is unlikely that this effect will generalise to all nicotine and tobacco products. For instance, research suggests that nicotine exposure from the nicotine patch when used alongside VLNC cigarettes leads to lower rates of smoking,[10 18] which may *facilitate* quit attempts. As such, to inform regulatory decisions, it is imperative to determine which alternative sources of nicotine affect cessation when using VLNC cigarettes and in what direction (ie, facilitate vs impede). It is suspected that several factors may come into play, particularly factors that would affect the reinforcing properties of smoking, such as the extent to which the product resembles a cigarette with regard to its sensory aspects and nicotine delivery and patterns of co-use (eg, simultaneous use as opposed to same day).

In summary, studies examining the impact of reduced nicotine content cigarettes on cessation may be affected by the availability of non-regulated cigarettes and other nicotine or tobacco products. Furthermore, enacting a nicotine standard that does not sufficiently reduce the nicotine content of cigarettes may impede cessation efforts. Of note, poorer cessation outcomes were seen with a relatively small increase in nicotine yield of VLNC cigarettes (from 0.05 to 0.09 mg). Thus, to maximise public health benefits, it is critical to reduce the nicotine yield of all cigarettes to the lowest possible level while encouraging reduced smoking.

What this study adds

- This is the first study to demonstrate that, when smoking very low nicotine content (VLNC) cigarettes, lower levels of nicotine exposure prior to a quit attempt enables cessation.
- Smoking high nicotine content cigarettes alongside VLNC cigarettes appeared to undermine nicotine reduction efforts and, in turn, reduce quit rates. Thus, the widespread availability of high nicotine content cigarettes may lead researchers to underestimate the public health impact of a nicotine reduction strategy due to non-compliance.
- Relatively small differences in the nicotine yield of VLNC cigarettes (0.05 vs 0.09 mg yield) appeared to impact cessation rates.

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